

# Design and Findings of the National Lung Screening Trial

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▶ Full Disclosure:

▶ No financial or other conflicts of interest



# National Lung Screening Trial (NLST)

## Design

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- ▶ Subjects randomized to low-dose CT (LDCT) or chest radiograph (CXR)
  - ▶ Three annual screening rounds for each arm
  - ▶ Total follow-up of 6-7 years
  - ▶ Diagnostic follow-up of positive screens –
    - ▶ No trial-wide algorithm
    - ▶ Study radiologists gave recommendations based on clinical judgment
  - ▶ Diagnostic follow-up and treatment conducted outside of trial auspices
  - ▶ Primary Outcome – lung cancer specific mortality
  - ▶ Secondary Outcomes – all cause mortality, lung cancer incidence and stage
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# NLST Eligibility Criteria

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- ▶ 30+ Pack Years
- ▶ Current Smoker or quit within 15 years
- ▶ Age 55-74
- ▶ No chest CT within past 18 months
- ▶ No prior lung cancer diagnosis



# Age and Smoking History Eligibility Criteria vs. NLST Experience

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Eligibility Criterion	NLST Population (N=53,454)	NLST Eligible Population, U.S. *
Current smoker, or former smoker who quit within 15 years	Current smoker: 48.2% Former smoker: 51.8% Quit within 4 yrs: 14.8% Quit 4-9.9 yrs: 17.2% Quit 10-15 yrs: 19.7%	Current smoker: 57.1%
30+ pack years	Median pack years: 48 25 <sup>th</sup> /75 <sup>th</sup> : 39/66	Median pack years: 47
Age 55-74 at entry	55-59: 42.8% 60-64: 30.6% 65-69: 17.8% 70-74: 8.8%	55-59: 35.2% 60-64: 29.3% 65-69: 20.8% 70-74: 14.7%

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\* - Estimated from Tobacco Use Supplement

# Radiologist Requirements

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- ▶ Certification by American Board of Radiology (or equivalent)
- ▶ Documented training in diagnostic radiology and radiation safety
- ▶ Involvement in supervision and interpretation of  $\geq 300$  chest CT acquisitions in the past 3 years
- ▶ Continuing medical education according to ACR standard
- ▶ Review of a dedicated NLST training set



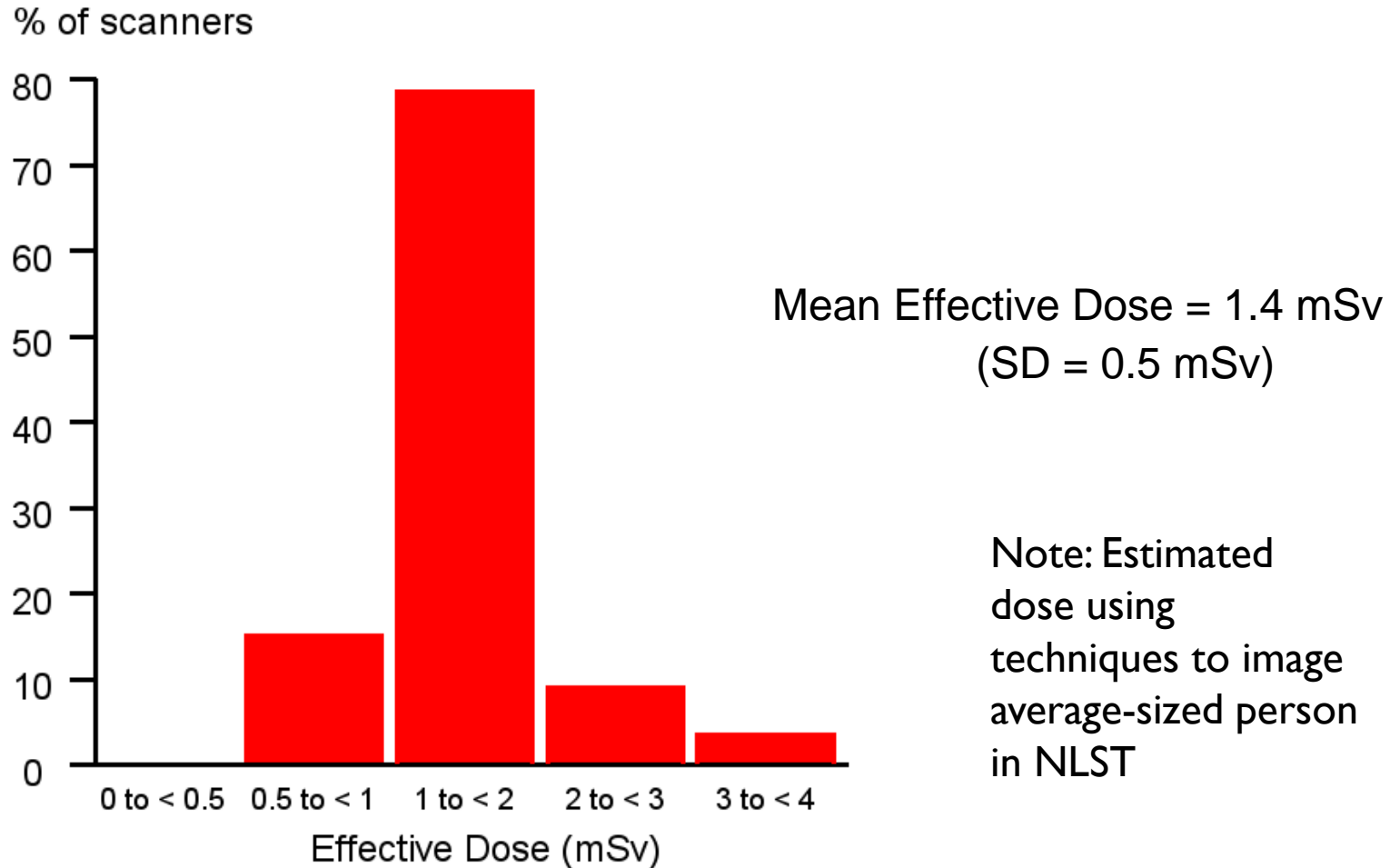
# NLST Protocol - CT Settings

Parameter	Values
Voltage (kVp)	120-140
Tube current-time product (mAs)	40-80 (dependent on participant body habitus)
Detector collimation (mm)	$\leq 2.5$
Reconstruction interval (mm)	1.0-2.5
Scanning time (sec)	$< 25$



# Effective Radiation Dose in NLST

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# LDCT Screen Positivity

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- ▶ Positive Screen Definition:
- ▶ Non-calcified nodule (NCN), maximum diameter  $\geq 4\text{mm}$
- ▶ OR
- ▶ other finding suspicious for lung cancer (e.g., lung consolidation, obstructive atelectasis)
- ▶ Final screen, NCN stable for 2 years → Negative result
- ▶ (at discretion of radiologist)
- ▶ Note: in practice, 98% of positive screens had a 4+mm non-calcified nodule



# NLST Results

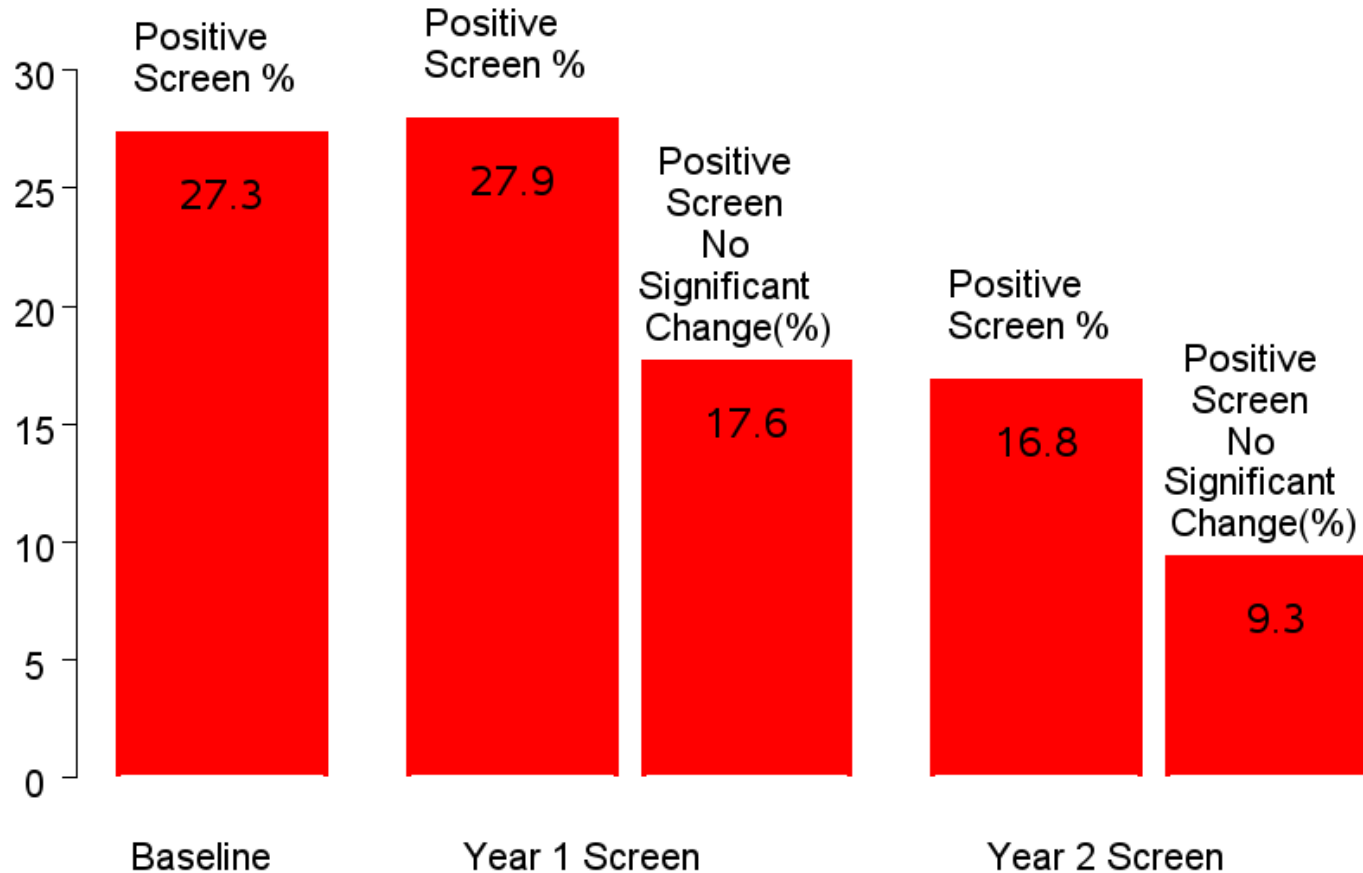
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- ▶ LDCT screen adherence & positivity
- ▶ Diagnostic follow-up of positive LDCT screens
- ▶ Lung cancer incidence & stage
- ▶ Mortality by trial arm (lung-cancer specific and all-cause)
- ▶ Screening center & radiologist factors
- ▶ Results by age



# LDCT Screening Results

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► Overall adherence to LDCT screening: 95%

# Diagnostic Follow-up of Positive LDCT Screens

	Baseline Screen			Year 1 & 2 Screens		
	No Cancer	Lung Cancer	All	No Cancer	Lung Cancer	All
	%	%	%	%	%	%
Any diagnostic follow-up	90.0	100	90.4	58.5	100	60.0
Chest radiography	17.3	41.5	18.2	11.0	34.6	11.9
Chest CT	73.3	67.0	73.1	33.1	68.1	34.3
Invasive procedure	3.7	98.5	7.2	2.3	98.4	5.7
[Surgical procedure]	1.3	76.7	4.2	0.9	84.4	3.8
Positive Predictive Value (PPV)			3.8			3.6
Complication of diagnostic follow-up	0.3	25.6	1.2	0.4	30.9	1.5



# Lung Cancer Incidence and Stage by Arm

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		LDCT Arm	CXR Arm
Total lung cancers	All	1060	941
	Screen Detected	649	279
Stage I Lung Cancers	All	520	289
	Screen Detected	400	131
Stage III/IV Lung Cancers	All	447	566

## Overdiagnosis:

Excess CT arm cancers  
as fraction of CT arm  
screen detected cancers

$$119/649 = 18.3\%$$



# Lung Cancer Specific Mortality

	<b>LDCT Arm</b>	<b>CXR Arm</b>	<b>Rate Ratio (95% CI)</b>	<b>Number Needed to Screen (95% CI)</b>
	Lung cancer deaths	Lung cancer deaths		
	# (Rate per 100,000 PY)	# (Rate per 100,000 PY)		
Jan 15 <sup>th</sup> , 2009 deadline	356 (247)	443 (309)	<b>0.80</b> (0.73-0.93)	307 (185-834)
Dec 31 <sup>st</sup> , 2009 deadline	469 (280)	552 (332)	<b>0.84</b> (0.75-0.95)	322 (182-1171)

Note: All subjects followed through Dec 31, 2009. Earlier deadline used for NEJM 2011 paper due to time constraints for endpoint verification



# All-cause mortality

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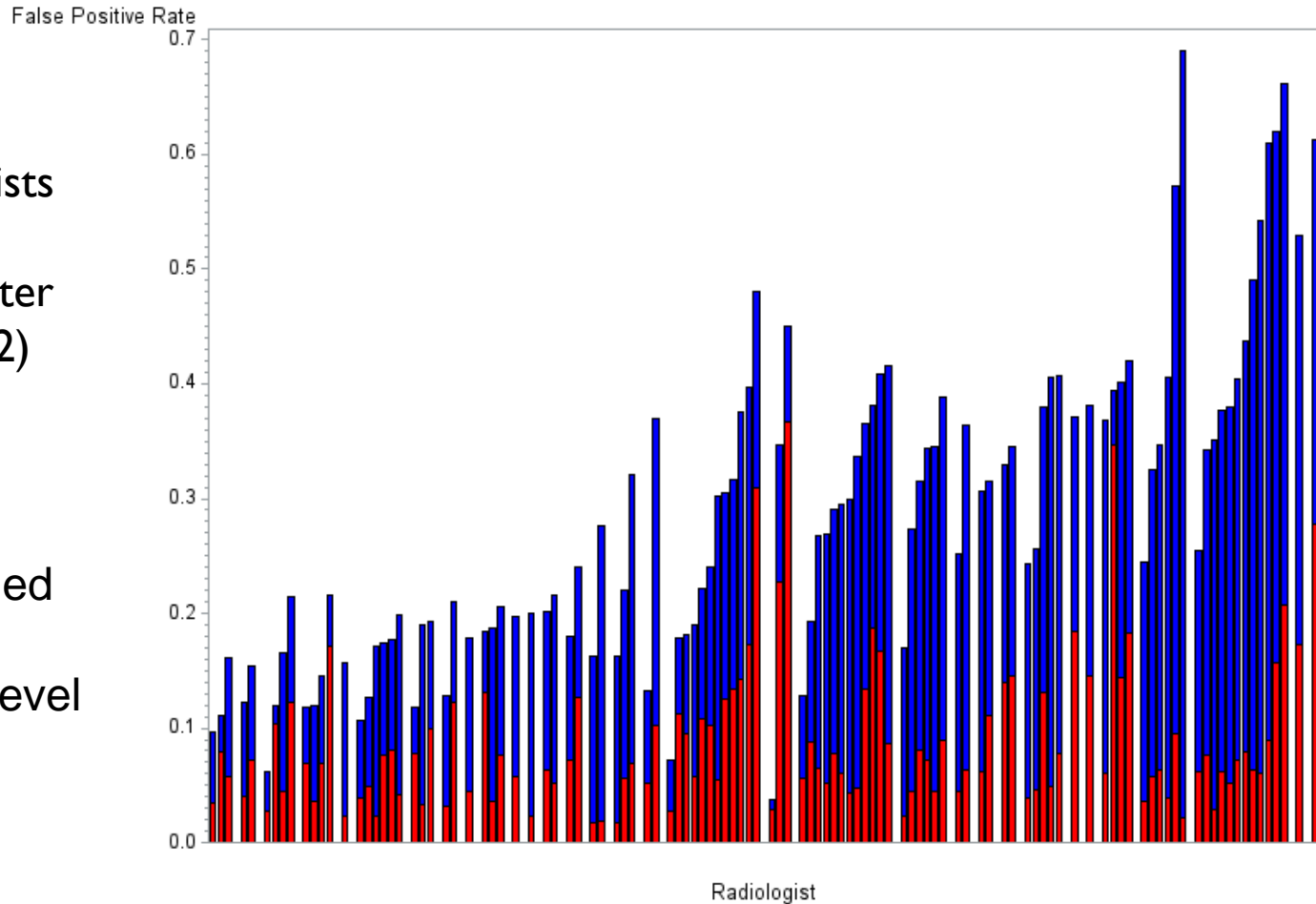
	<b>LDCT Arm</b>	<b>CXR Arm</b>	<b>Rate Ratio (95% CI)</b>
Total Deaths	1877	2000	0.933 (0.86-0.99)
Total deaths excluding lung cancer	1450	1497	0.968 (0.97-1.04)



# Radiologist and Center Variability in False Positive Rates

Rates for 112  
NLST Radiologists  
with 100+ CTs  
grouped by center  
(Radiology, 2012)

Recommended  
Follow-up  
Red: High Level  
Blue: Other



# Radiologist Recommendations

## Follow-up of Baseline LDCT Positive Screen

	Size (max diameter) of largest nodule Solid nodules only			
	4-6 mm	7-9mm	10-14 mm	15+ mm
Recommendation	%	%	%	%
No procedure before 12 months	6.4	1.0	0.6	0.5
Other	3.4	3.3	5.6	6.1
LDCT at 6 months	46.8	33.3	16.6	6.1
LDCT at 3-6 months	22.1	25.1	9.4	4.0
LDCT at 3 months	18.4	25.5	20.2	12.1
Diagnostic CT, Contrast-enhanced CT, or FDG/PET	2.5	9.9	34.7	42.0
Biopsy	0.5	2.0	13.0	29.3

# Academic vs. Non-Academic Sites in NLST

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	Academic Sites	Non-academic Sites
Number of Centers	26	7
Number of Radiologists *	66	46
Percentage of Subjects	65%	35%
LDCT Specificity (aggregate)	77.8%	74.0%
LDCT Sensitivity (aggregate)	92.1%	95.1%

Note: diagnostic follow-up and treatment not necessarily performed at screening center

\* - With 100+ CT Reads

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# Major Findings by Age 55-64 versus 65+

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	Age 55-64	Age 65+	P-value
Adherence to LDCT Screening (%)	95.2%	95.1%	0.7
Positive LDCT screen rate (%)	22.5	27.6	<0.0001
Significant abnormality, non-lung Ca (%)	6.9	8.7	<0.0001
Positive Predictive Value (%)	2.8	4.9	<0.0001
Complications of diagnostic F/U (% of positive screens) *	0.31	0.42	0.2
Rate Ratio: LDCT arm versus CXR arm			
Lung-cancer mortality	0.82	0.87	0.6
All-cause mortality	0.942	0.918	0.7

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► \* - No lung cancer diagnosis

# Extending from 3 annual screens (NLST) to long-term population annual screening

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- ▶ **Arguments in favor of :**
- ▶ Trial screening scenarios often based on logistics of the trial, not on intended population regimens
- ▶ Mammography – when Medicare coverage introduced, trials had at most 5-6 screening rounds
- ▶ Problem of tracking CT screens prior to Medicare entry
- ▶ Harms (false positives, overdiagnosis, radiation) can in large part be projected from shorter screening regimens
- ▶ Modeling efforts have attempted to extrapolate benefits (& harms) to longer term screening



# Extending from 3 annual screens (NLST) to long-term population annual screening

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- ▶ **Caveats:**
- ▶ NLST was one third prevalence screens; long-term population screening primarily incidence (repeat) screens
- ▶ NLST had only 1 of 3 rounds with 2 year nodule history on CT, population screens generally would have 2 year CT nodule history
- ▶ Models that extrapolate benefit (and harms) must be viewed with caution
- ▶ Long-term adherence with screening unknown

